regarding the theoretical benefit of combination antiretroviral drugs for the neonate, potential risks, and available data on appropriate dosing. She should also be informed that use of antiretroviral drugs in addition to ZDV for newborn prophylaxis is of unknown efficacy in reducing risk of perinatal transmission.

Scenario #3: HIV-Infected Women in Labor Who Have Had No Prior Therapy

Recommendation

Several effective regimens are available (**Table 4**). These include the following:

1. single dose nevirapine at the onset of labor followed by a single dose of nevirapine for the newborn at age 48 hours;
2. oral ZDV and 3TC during labor, followed by one week of oral ZDV/3TC for the newborn;
3. intrapartum intravenous ZDV followed by six weeks of ZDV for the newborn; and
4. the two-dose nevirapine regimen combined with intrapartum intravenous ZDV and six week ZDV for the newborn.

In the immediate postpartum period, the woman should have appropriate assessments (e.g., $CD4^+$ count and HIV-1 RNA copy number) to determine whether antiretroviral therapy is recommended for her own health.

Discussion

While intrapartum antiretroviral drug medications will not prevent perinatal transmission that occurs before labor, most transmission occurs near to the time of or during labor and delivery. Pre-exposure prophylaxis can be provided by administration of a drug to the mother that rapidly crosses the placenta to produce systemic antiretroviral drug levels in the fetus during intensive exposure to HIV in maternal genital secretions and blood during birth.

Several intrapartum/neonatal antiretroviral prophylaxis regimens are applicable for women in labor who have had no prior antiretroviral therapy **(Table 4)**. Two regimens, one using a two-dose regimen of nevirapine and the other a combination ZDV and 3TC regimen, were shown to reduce perinatal transmission in randomized clinical trials in breastfeeding settings, while available epidemiologic data suggest efficacy of a third, ZDV-only regimen. The fourth regimen, combining ZDV with nevirapine, is based upon theoretical considerations.

In the HIVNET 012 trial, conducted in Uganda, a single dose of oral nevirapine given to women at the onset of labor and a single dose to the infant at age 48 hours was compared to oral ZDV given to the woman every three hours during labor and postnatally to the infant for seven days **(Table 4)**. At age six weeks, the rates of transmission were 12% (95% CI, 8–16%) in the nevirapine arm compared to 21% (95% CI, 16–26%) in the ZDV arm, a 47% reduction (95% CI, 20–64%) in transmission *[63]*. No significant short-term toxicity was observed in either group. Because there was no placebo group, no conclusions can be drawn regarding the efficacy of the intrapartum/one week neonatal ZDV regimen compared to no treatment.

In the PETRA trial, conducted in Uganda, South Africa and Tanzania, ZDV and 3TC were administered orally intrapartum and to the woman and infant for seven days postnatally. Oral ZDV and 3TC were given at the onset of labor and continued until delivery **(Table 4)**. Postnatally, the woman and infant received ZDV and 3TC every 12 hours for seven days. At age six weeks, the rates of transmission were 9% in the ZDV/3TC arm versus 15% in the placebo arm, a 40% reduction in transmission *[62]*. However, no differences in transmission were observed when oral ZDV and 3TC were administered only during the intrapartum period (transmission of 14% in the ZDV/3TC and 15% in the placebo arm), indicating that some post-exposure prophylaxis is needed, at least in breastfeeding settings.

These clinical trials were conducted in Africa, where the majority of women breastfeed their infants. Because HIV can be transmitted by breast milk and the highest risk period for such transmission is the first few months of life *[107]*, the absolute transmission rates observed in the African trials may not be comparable to what might be observed with these regimens in HIV-infected women in the U.S., where breastfeeding is not recommended. However, comparison of the percent reduction in transmission at early timepoints (e.g., four to six weeks) may be applicable. In the effective arms of the PETRA trial, antiretrovirals were administered postnatally to the mother as well as the infant to reduce the risk of early breastmilk transmission. In the United States, administration of ZDV/3TC to the mother postnatally in addition to the infant would not be required for prophylaxis against transmission because HIV-infected women are advised not to breastfeed their infants (although ZDV/3TC might be indicated as part of a combination postnatal treatment regimen for the woman).

Epidemiologic data from New York State indicate that intravenous maternal intrapartum ZDV followed by

oral ZDV for six weeks to the infant may significantly reduce transmission compared to no treatment **(Table 4)**. Transmission rates were 10% (95% CI [CI], 3–22%) with intrapartum and neonatal ZDV compared to 27% (95% CI, 21–33%) in the absence of ZDV, a 62% reduction in risk (95% CI, 19–82%) *[68, 69]*. Similarly, in epidemiologic study in North Carolina, intravenous intrapartum and six week oral neonatal ZDV treatment was associated with a transmission rate of 11%, compared to 31% without therapy *[6]*. However, intrapartum ZDV combined with very short postnatal infant ZDV administration, such as the one-week postnatal infant ZDV course in HIVNET 012 *[63]*, has not proven effective to date. This underscores the necessity of recommending a full six week course of infant treatment when ZDV alone is utilized.

There are currently no data to address the relative efficacy of these three intrapartum/neonatal antiretroviral regimens for prevention of transmission. There is overlap in the 95% CI for the two-dose nevirapine regimen and the maternal intravenous intrapartum/six week infant oral ZDV regimen. In the absence of data to suggest the superiority of one or more of the possible regimens, choice should be based upon the specific circumstances of each woman. The two-dose nevirapine regimen offers the advantage of lower cost, the possibility of directly observed therapy and increased adherence compared to the other two regimens. In South Africa, a clinical trial (SAINT) compared the two-dose nevirapine and the intrapartum/postpartum ZDV/3TC regimens. No significant differences were observed between the two regimens in terms of efficacy in reducing transmission or in maternal and infant toxicity *[64]*.

Whether combining intravenous intrapartum/six week neonatal oral ZDV with the two-dose nevirapine regimen will provide additional benefit over that observed with each regimen alone is unproven. Clinical trial data have clearly established that combination is superior to single drug therapy for treatment of established infection, although data to show superiority of combination treatment when used for prevention of transmission are not available. However, infants born to women in labor who have not received any antiretroviral therapy are at high risk for infection. The two-dose nevirapine regimen had no significant short-term drug-associated toxicity in the 313 mother-infant pairs exposed to the regimen in the HIVNET 012 trial. Nevirapine and ZDV are synergistic in inhibiting HIV replication in vitro *[108]*, and both nevirapine and ZDV rapidly cross the placenta to achieve drug levels in the infant nearly equal to those in the mother. In contrast to ZDV, nevirapine can decrease plasma HIV-1 RNA concentration by at least 1.3 log by seven days after a single dose *[109]* and is active immediately against intracellular and extracellular virus *[110]*. However, nevirapine resistance can be induced by a single mutation at codon 181, whereas high-level resistance to ZDV requires several mutations.

A theoretical benefit of combining the intrapartum/neonatal ZDV and nevirapine regimens includes potential efficacy if the woman had acquired infection with HIV that is resistant to either ZDV or nevirapine. Perinatal transmission of antiretroviral drug-resistant virus has been reported but appears to be unusual *[6, 106, 111, 112]*. Virus with low-level ZDV resistance may be less likely to establish infection than wild type, and transmission may not occur even when maternal virus has high-level ZDV resistance *[112-115]*. Since the prevalence of drug-resistant virus is an evolving phenomenon, surveillance is needed to determine the prevalence of drug-resistant virus in pregnant women over time and the risk of transmission of resistant viral strains. The potential benefits of combination prophylaxis with intrapartum/neonatal nevirapine and ZDV must be weighed against the increased cost, possible adherence issues, potential short and long-term toxicity, and the lack of definitive data to show that the combination offers any additional benefit for prevention of transmission compared to use of either drug alone.

Scenario #4: Infants Born to Mothers Who Have Received No Antiretroviral Therapy During Pregnancy or Intrapartum

Recommendation

The 6-week neonatal ZDV component of the ZDV chemoprophylactic regimen should be discussed with the mother and offered for the newborn. ZDV should be initiated as soon as possible after delivery—preferably within 6–12 hours of birth. Some clinicians may choose to use ZDV in combination with other antiretroviral drugs, particularly if the mother is known or suspected to have ZDV-resistant virus. However, the efficacy of this approach for prevention of transmission is unknown, and appropriate dosing regimens for neonates are incompletely defined. In the immediate postpartum period, the woman should undergo appropriate assessments (e.g., $CD4^+$ count and HIV-1 RNA copy number) to determine if antiretroviral therapy is required for her own health. The infant should undergo early diagnostic testing so that if HIV-infected, treatment can be initiated as soon as possible.